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Enantioselective Carbon–Sulfur Bond Formation: γ Additions of Aryl Thiols to Allenates Catalyzed by a Chiral Phosphine

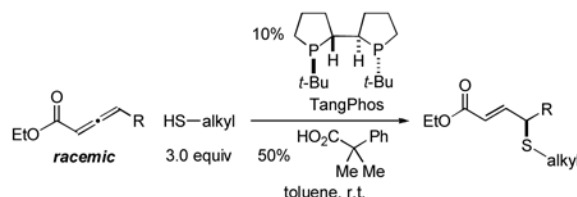
Yuji Fujiwara, Jianwei Sun, and Gregory C. Fu*

Abstract

An effective phosphine-catalyzed method has been developed for the enantioselective addition of aryl thiols to the γ position of allenates, thereby furnishing ready access to aryl alkyl sulfides in very good ee. An array of mechanistic data are consistent with addition of the chiral phosphine to the allenate being the turnover-limiting step of the catalytic cycle. The optimized reaction conditions, as well as the mechanistic observations, differ markedly from an earlier report on asymmetric additions of *alkyl* thiols to allenates, which highlights the potential for divergent behavior between alkyl and aryl thiols when serving as nucleophiles.

As phosphines have emerged as versatile nucleophilic catalysts, the use of chiral phosphines to control the enantioselectivity of various processes has begun to be pursued with substantial vigor.¹ One example of a phosphine-catalyzed transformation with significant potential utility in organic synthesis is the γ functionalization of electron-poor allenes and alkynes with carbon, nitrogen, oxygen, and sulfur nucleophiles.² Recently, the first asymmetric variants of such processes have been described.^{3,4}

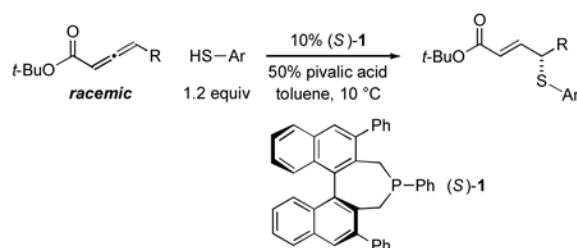
In 2010, we reported the only example of a phosphine-catalyzed γ functionalization of a carbonyl compound with a sulfur nucleophile (the addition of alkyl thiols to allenates), and we demonstrated that this process can be achieved with high enantioselectivity in the presence of a chiral bisphosphine [Eq. (1)].^{4c} This method complements previous catalytic asymmetric routes to α - and β -thio-substituted carbonyl compounds.⁵ Unfortunately, under the same conditions, aryl thiols do not add in high ee or good yield (Eq. (1): 70% ee and 9% yield with PhSH and R = *n*-Pr).⁶ Due to the significance of aryl alkyl sulfides,⁷ addressing this deficiency is an important objective. In this report, we establish that the use of a chiral monophosphine enables a catalytic asymmetric route to aryl alkyl sulfides through the γ addition of aryl thiols to allenates [Eq. (2)].⁸



(1)

*Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139 (USA). Fax: (+1) 617-324-3611; Tel: (+1) 617-253-2664; gcf@mit.edu.

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(2)

In preliminary studies, we investigated the utility of a range of chiral phosphines, including those that have proved useful in other γ additions, as catalysts for the enantioselective γ addition of an aryl thiol to an allenolate (Table 1, entries 1–5). From this initial survey, a monophosphine, phosphepine **2**,⁹ emerged as the most promising catalyst, although the ee and the yield of the aryl alkyl sulfide were only moderate (entry 2). In contrast, for the asymmetric addition of *alkyl* thiols to allenolates, a *bis*phosphine was determined to be the catalyst of choice (TangPhos; Eq. (1)).

Incorporating groups into the 3,3' positions of 1,1'-binaphthyl derivatives is an effective strategy for increasing the effectiveness of a diverse set of chiral catalysts.¹⁰ Very recently, we established for the first time that this approach is also useful in the context of asymmetric nucleophilic catalysis with chiral phosphepines, specifically, for enantioselective formal [3+2] cycloadditions catalyzed by **1** vs. **2**.¹¹ We have been pleased to determine that for asymmetric γ additions of aryl thiols, an entirely different process, this strategy also leads to a substantial enhancement in both ee and yield (entry 2 vs. entry 6).

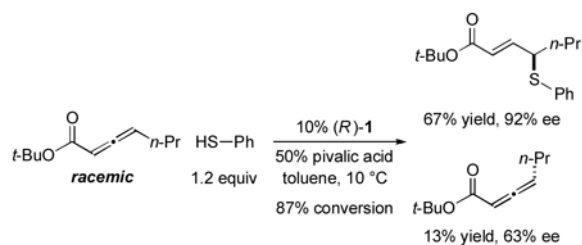
Additional information on the impact of various parameters on the course of this catalytic asymmetric synthesis of aryl alkyl sulfides is provided in Table 1. In contrast to the phosphine-catalyzed enantioselective additions of oxygen^{4a} and carbon^{4b,d} nucleophiles that have been reported, in the case of thiol nucleophiles, the chiral catalyst must out-compete a significant background reaction--uncatalyzed conjugate addition of the thiol to the β carbon of the allenolate.^{4c} In the absence of phosphepine **1**, no γ addition is observed (entries 7 and 8), whereas, if the reaction is conducted in the presence of catalyst **1** but in the absence of pivalic acid, then a moderate ee and a low yield are obtained (entry 9). The reaction can be performed with a smaller substituent on the ester (R; entry 10) or at room temperature (entry 11) with only a slight erosion in efficiency.

Phosphepine **1** catalyzes asymmetric C–S bond formation between aryl thiols and a variety of allenolates (Table 2).¹² Thus, the γ substituent of the allenolate can range in size from methyl to isopropyl, and the allene can bear functional groups such as an olefin, a silyl ether, an ester, or a halogen.

The scope of this method for the catalytic enantioselective synthesis of aryl alkyl sulfides is also broad with respect to the aryl thiol (Table 3). Thus, ortho-, meta-, and para-substituted, as well as electron-rich and electron-poor, aryl thiols add to allenolates in good ee and yield. An unprotected amino group is compatible with the reaction conditions (entry 7).

During the course of a phosphepine-catalyzed enantioselective γ addition of an aryl thiol to an allenolate, the resting state of the catalyst is the phosphine itself, not the protonated catalyst or a phosphepine–allenolate adduct (³¹P NMR spectroscopy). The rate law for the process is first order in the catalyst and the allenolate and zero order in the thiol and pivalic acid. During the reaction, the ee of the product is constant, but a modest kinetic resolution of

the unreacted allene is observed [Eq. (3)].¹³ Collectively, these data are consistent with a rate-determining irreversible 1,4-addition of the phosphine catalyst to the allenolate (Figure 1).



(3)

Some of these mechanistic observations stand in intriguing contrast to those made for the asymmetric γ addition of *alkyl* thiols to allenolates catalyzed by TangPhos.^{4c} For those reactions, a catalyst-substrate adduct *is* the resting state of the catalytic cycle, and *no* kinetic resolution of the starting allenolate is observed. These differences point to a delicate balance among the rates of the various steps of the catalytic cycles for phosphine-catalyzed γ additions.¹⁴

In summary, we have developed an effective method for the catalytic asymmetric addition of aryl thiols to the γ position of allenolates, overcoming the usual propensity of these two partners to bond β to the ester. This process provides ready access to aryl alkyl sulfides in good ee, and it complements earlier catalytic enantioselective processes in which sulfur substituents are introduced at the α and β positions of carbonyl compounds and in which *alkyl* thiols are incorporated at the γ position. A wide array of mechanistic data are consistent with the addition of the chiral phosphine to the allene as the rate-determining step of the catalytic cycle. The difference in the optimized reaction conditions (eq 1 vs. eq 2), as well as in the mechanistic observations, attest to the potential for divergent behavior when *alkyl* thiols and aryl thiols serve as nucleophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

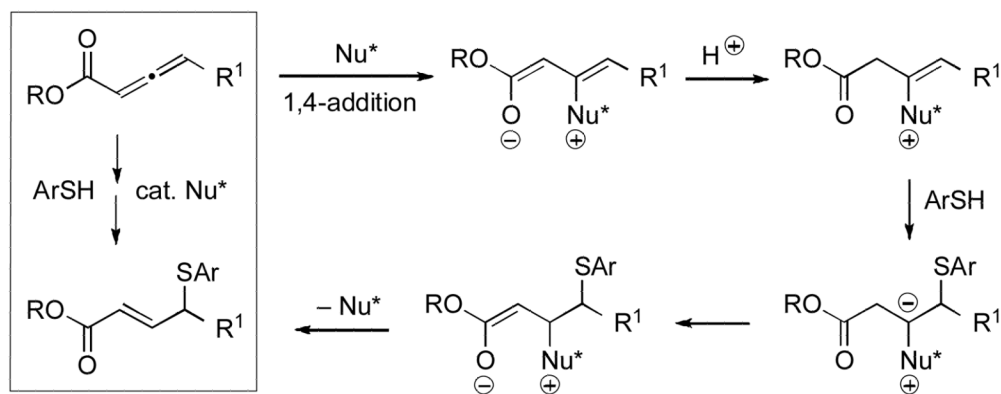
Acknowledgments

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Notes and references

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8. Allenates can be synthesized in one step through the treatment of an acid chloride with a commercially available olefinating reagent such as (carbethoxymethylene)triphenylphosphorane.
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12. Notes: a) The phosphine oxide of phosphepine **1** does not serve as a catalyst for the γ addition of aryl thiols to allenates; b) On a gram scale, the reaction illustrated in entry 6 of Table 3 proceeded in 92% ee and 72% yield; c) The rate of the γ addition is not highly sensitive to water, e.g., the addition of five equivalents of water to the reaction depicted in entry 6 of Table 3 led to formation of the desired product in 87% ee and 76% yield; d) Under our standard conditions, a hydroxyl-, a nitro-, a carboxyl-, and an acetamino-substituted aryl thiol, as well as a heteroaryl thiol, were not very effective reaction partners; e) In the presence of 5% phosphepine **1** and 25% pivalic acid (one-half of the standard catalyst loading), the γ addition illustrated in entry 6 of Table 3 proceeded in 88% ee and 67% yield; f) Additives other than pivalic acid were also examined. Use of any of an array of carboxylic acids (RCO_2H , where R is an unfunctionalized alkyl group or aryl group) led to slightly diminished ee's (within ~5%) and modest-to-substantial erosion in yields. Attempts to employ a hydroxamic acid, a sulfonic acid, or a phenol as the additive resulted in significantly lower ee's and yields.
13. We are aware of only one other example of a kinetic resolution during a phosphine-catalyzed γ -addition reaction (Ref. 4d).
14. The divergent behavior between the two processes may be attributable in part to the bidentate (TangPhos) versus monodentate (phosphepine **1**) nature of the two phosphine catalysts. Indeed, we have determined that truncated monophosphines that are structurally related to TangPhos furnish very different results as compared with TangPhos itself.

**Fig. 1.**

A possible pathway for the nucleophile-catalyzed enantioselective γ addition of an aryl thiol to an allenolate (for simplicity, the elementary steps are drawn as irreversible, and one E/Z isomer of the intermediates is illustrated).

Table 1Catalytic asymmetric γ addition of an aryl thiol to an allenolate: Effect of reaction parameters^a

entry	change from the “standard conditions”	ee (%)	yield (%) ^b
1	TangPhos, instead of (S)-1	31	11
2	(S)-2, instead of (S)-1	52	66
3	(S)-3, instead of (S)-1	30	24
4	(S)-4, instead of (S)-1	50	8
5	(S)-5, instead of (S)-1	71	46
6	none	90	81
7	no (S)-1 and no pivalic acid	–	<2 _c
8	no (S)-1	–	<2 _c
9	no pivalic acid	72	28
10	R = Et	88	75
11	r.t.	88	78

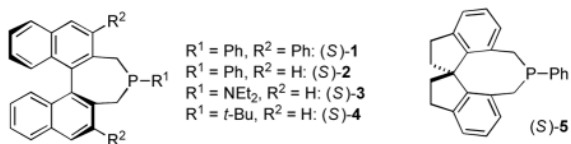
^a All data are the average of two experiments.^b The yield was determined by ¹H NMR analysis with the aid of an internal standard.^c Major product: β addition of the thiol.

Table 2Catalytic asymmetric γ additions of aryl thiols to allenates: Variation of the allenate^a

<p> $t\text{-BuO}-\text{C}(=\text{O})-\text{CH}=\text{C}(\text{R})-\text{CH}_2-\text{CHO}$ (racemic) + $\text{HS}-\text{Ar}$ (1.2 equiv) $\xrightarrow[72\text{ h}]{10\% (\text{S})\text{-1, 50\% pivalic acid, toluene, } 10\text{ }^\circ\text{C}}$ $t\text{-BuO}-\text{C}(=\text{O})-\text{CH}=\text{C}(\text{R})-\text{CH}(\text{S}-\text{Ar})-\text{CHO}$ </p> <p>Ar = 4-<i>t</i>-butylphenyl</p>			
entry	R	ee (%)	yield (%) ^b
1	Me	81	58
2	<i>n</i> -Pr	91	81
3		91	68
4 ^c	<i>i</i> -Pr	94	61
5		91	70
6		89	71
7		95	68
8		91	75
9		90	66

^a All data are the average of two experiments.^b Yield of purified product.^c Run at r.t.

Table 3Catalytic asymmetric γ additions of aryl thiols to allenates: Variation of the aryl thiol^a

entry	R	ee (%)	yield (%) ^b
1	H	90	73
2	2-OMe	90	67
3	3,5-dimethyl	92	81
4	4-F	91	64
5	4-Cl	91	59
6	4-OMe	91	76
7	4-NH ₂	86	64

^a All data are the average of two experiments.^b Yield of purified product.